Exhibit 7

JAMA | Original Investigation

Association of Powder Use in the Genital Area With Risk of Ovarian Cancer

Katie M. O'Brien, PhD; Shelley S. Tworoger, PhD; Holly R. Harris, ScD; Garnet L. Anderson, PhD; Clarice R. Weinberg, PhD; Britton Trabert, PhD; Andrew M. Kaunitz, MD; Aimee A. D'Aloisio, PhD; Dale P. Sandler, PhD; Nicolas Wentzensen, MD, PhD

IMPORTANCE The relationship between use of powder in the genital area and ovarian cancer is not established. Positive associations reported in case-control studies have not been confirmed in cohort studies.

OBJECTIVE To estimate the association between use of powder in the genital area and ovarian cancer using prospective observational data.

DESIGN, SETTING, AND PARTICIPANTS Data were pooled from 4 large, US-based cohorts: Nurses' Health Study (enrollment 1976; follow-up 1982-2016; n = 81 869), Nurses' Health Study II (enrollment 1989; follow-up 2013-2017; n = 61 261), Sister Study (enrollment 2003-2009; follow-up 2003-2017; n = 40 647), and Women's Health Initiative Observational Study (enrollment 1993-1998; follow-up 1993-2017; n = 73 267).

EXPOSURES Ever, long-term (≥20 years), and frequent (≥1/week) use of powder in the genital area.

MAIN OUTCOMES AND MEASURES The primary analysis examined the association between ever use of powder in the genital area and self-reported incident ovarian cancer. Covariate-adjusted hazard ratios (HRs) and 95% CIs were estimated using Cox proportional hazards models.

RESULTS The pooled sample included 252 745 women (median age at baseline, 57 years) with 38% self-reporting use of powder in the genital area. Ten percent reported long-term use, and 22% reported frequent use. During a median of 11.2 years of follow-up (3.8 million person-years at risk), 2168 women developed ovarian cancer (58 cases/100 000 person-years). Ovarian cancer incidence was 61 cases/100 000 person-years among ever users and 55 cases/100 000 person-years among never users (estimated risk difference at age 70 years, 0.09% [95% CI, −0.02% to 0.19%]; estimated HR, 1.08 [95% CI, 0.99 to 1.17]). The estimated HR for frequent vs never use was 1.09 (95% CI, 0.97 to 1.23) and for long-term vs never use, the HR was 1.01 (95% CI, 0.82 to 1.25). Subgroup analyses were conducted for 10 variables; the tests for heterogeneity were not statistically significant for any of these comparisons. While the estimated HR for the association between ever use of powder in the genital area and ovarian cancer risk among women with a patent reproductive tract was 1.13 (95% CI, 1.01 to 1.26), the *P* value for interaction comparing women with vs without patent reproductive tracts was .15.

CONCLUSIONS AND RELEVANCE In this analysis of pooled data from women in 4 US cohorts, there was not a statistically significant association between use of powder in the genital area and incident ovarian cancer. However, the study may have been underpowered to identify a small increase in risk.

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Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Katie M. O'Brien, Epidemiology Branch, National Institute of Environmental Health Sciences, Research Triangle Park, NC, 27709 (obrienkm2@niehs.nih.gov).

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Some women apply powder to their genitals, either through direct application or on underwear, sanitary napkins, diaphragms or tampons. Most powder products include some mineral talc.[1] Talc was first investigated as a carcinogen based on its relationship to asbestos, which has known carcinogenic effects[2] and may be mined in the same locations. However, all US-based manufacturers of cosmetic talc agreed to ban asbestos in 1976,[3] and the International Agency for Research on Cancer has since concluded there is only "possible" evidence that perineal use of talc-based body powder may be carcinogenic.[1]

This classification was largely based on evidence from observational studies. Case-control studies have reported positive associations between ever use of powder in the genital area and ovarian cancer, with an estimated odds ratio of 1.24 in a pooled analysis[4] and 1.31 in a meta-analysis.[5] However, these findings may be affected by recall bias,[6,7] and a recent surge in talc-related lawsuits and media coverage[8,9] has increased this possibility. Thus, it is crucial to evaluate the talc-ovarian cancer association using prospective data.

To date, 3 large cohort studies have assessed the association between use of powder in the genital area and ovarian cancer risk, with inconsistent results.[10-12] However, ovarian cancer is a rare disease (1.3% lifetime risk in the United States),[13] and individual cohort studies are not sufficiently powered to detect modest associations, particularly if restricted to susceptible subgroups, such as women with patent reproductive tracts (ie, having an intact uterus and no tubal ligation).

To better examine the association between use of powder in the genital area and risk of ovarian cancer, 4 large US cohorts that collected the necessary information were identified: the Nurses' Health Study (NHS), Nurses' Health Study II (NHSII), Sister Study (SIS), and Women's Health Initiative Observational Study (WHI-OS). While associations between genital use of powder and ovarian cancer risk have been reported for 3 of these (NHS, WHI-OS, and SIS),[10-12] the pooled results reported here incorporate updated data, including additional cases and longer follow-up.

Key Points

Question Is use of powder in the genital area associated with the risk of developing ovarian cancer?

Findings In this analysis that pooled data from 4 cohorts with a total of 252 745 women, the hazard ratio for the association between self-reported ever use vs never use of powder in the genital area and incident ovarian cancer was 1.08 (95% CI, 0.99-1.17).

Meaning Among women from 4 prospective cohorts, there was not a statistically significant association between use of powder in the genital area and ovarian cancer, but the study may have been underpowered to identify a small increase in risk.

Methods

Study Sample

The study designs of these 4 US-based cohorts have been described in detail elsewhere.[14-16] Briefly, the NHS (n = 121 700) enrolled registered nurses living in the United States in 1976, and the NHSII (n = 116 429) did the same in 1989. The study protocols were approved by the institutional review boards of the Brigham and Women's Hospital, the Harvard T.H. Chan School of Public Health, and those of participating registries, as required. All participants provided written, informed consent. Although the initial questionnaires did not ask about genital use of powder, participants were queried about powder use on the 1982 NHS and 2013 NHSII questionnaires. We only included follow-up time after the questionnaire about use of powder in the genital area was administered and will refer to the questionnaire that assessed powder use as baseline to maintain consistent language across all 4 studies.

Genital use of powder was assessed at enrollment for SIS between 2003 and 2009 (n = 50 884) and for WHI-OS between 1993 and 1998 (n = 93 676). Women were eligible for SIS if they had a sister previously diagnosed with breast cancer but had no personal diagnosis of breast cancer at enrollment. Eligible participants in WHI-OS were postmenopausal women who resided near one of 40 clinical centers. Both studies were approved by the relevant institutional review boards and all participants provided written, informed consent.

Exposure Assessment

The cohorts differed in how they asked participants about use of powder in the genital area (eAppendix in the Supplement). NHS participants were asked whether they "ever commonly used talcum, baby powder or deodorizing powder" on their "perineal (private) area" (no, <1/week, 1-6 times/week, daily) or on sanitary napkins (yes/no). The NHSII questionnaire asked women to report use only if it occurred at least weekly in the "genital/rectal area or on sanitary napkins, tampons, or underwear" and if so, for how long (<1 year, 1-<10 years, 10-<20 years, 20-<30 years, 30+ years). In SIS, the question specifically focused on use of talcum powder and application to "a sanitary napkin, underwear, diaphragm, or cervical cap, or directly to the vaginal area" in the last year or at the ages of 10 to 13 years. Participants were queried about their frequency of use in the year prior to enrollment (never, <1/mo, 1-3 times/mo, 1-5 times/week, >5 times/week), as well as use during the ages 10-13 (did not use, sometimes, frequently). Women in WHI-OS were asked if they had ever used powder on their "private parts (genital areas)" (yes/no) and for how long they had used it (<1 year, 1-4 years, 5-9 years, 10-19 years, 20+ years), with similar questions for powder use on diaphragms or sanitary pads.

To harmonize across the 4 studies, we defined women as ever vs never users of powder on genital areas. For SIS, ever use included use in the last year or at ages 10 to 13 years. We were also able to examine long-term use, which we defined as use of powder on genitals for at least 20 years (NHSII and WHI-OS) or use at ages 10 to 13 years and also in the last year (SIS). Frequent users were those who reported use of powder in the

genital area at least once per week (NHS, NHSII), at least once per week in the last year, or "frequently" during ages of 10 to 13 years (SIS).

Outcome Assessment

For NHS and NHSII, follow-up questionnaires were distributed every 2 years, at which point participants were asked to report recent cancer diagnoses. Those reporting incident cancers were asked to grant access to their medical records, which were reviewed for confirmation of the diagnosis and disease details. Additional cases were identified from among deceased participants via National Death Index searches. The protocol for SIS was similar, except follow-up questionnaires were collected annually and most participants provided pathology reports rather than complete medical records. Participants in WHI-OS were also asked to self-report cancers on annual questionnaires, but only medically confirmed cases were counted. All 4 studies categorized tumors originating in the ovary, peritoneum, and fallopian tubes as ovarian cancers.

For NHS, NHSII, and SIS, delays in the confirmation process and incomplete retrieval of medical records meant that not all self-reported cases could be medically confirmed. We ran sensitivity analyses limited to medically confirmed cases but included all self-reported diagnoses in our main analyses. Subtype analyses were limited to medically confirmed cases.

Covariates

All 4 studies had substantial covariate data, which we harmonized into a common set of potential confounders or effect modifiers. The following data were included: age at baseline (continuous), race (white, black, other), education (≤high school, some college, completed college), body mass index (BMI [calculated as weight in kilograms divided by height in meters squared], restricted cubic spline), parity (nulliparous, 1 birth, 2 births, ≥3 births), smoking status (never, former, current), oral contraceptive use (ever/never), hormone therapy use (ever/never), tubal ligation status (yes/no), hysterectomy status (yes/no), and menopausal status (premenopausal/postmenopausal). Race was self-reported by the participant, based on provided categories. It was considered to be an important confounder because both ovarian cancer rates[13] and genital powder use vary by race/ethnicity. Only baseline levels of these covariates were considered as confounders, though we did consider post-baseline changes in menopausal status when assessing effect modification.

Statistical Analyses

We used Cox proportional hazards models with age as the primary time scale to estimate hazard ratios (HRs) and 95% CIs measuring the association between genital use of powder and incident ovarian cancer, adjusting for potential confounders. We selected potential confounders using a directed acyclic graph framework,[17] considering covariates that were possibly related to use of powder in the genital area and also ovarian cancer risk.

We excluded women who had ovarian cancer or a bilateral oophorectomy prior to baseline, or who were missing information on powder use or age at ovarian cancer diagnosis. For regression analyses, we additionally excluded women with missing data for 1 or more covariates. Women underwent follow-up from age at baseline until ovarian cancer diagnosis, with censoring at bilateral oophorectomy, end of follow-up, or death from causes other than ovarian cancer. An exception was made for WHI-OS because postbaseline oophorectomy data were not collected. Participants in SIS and WHI-OS who were no longer actively responding to follow-up requests were censored at age of last contact, although their follow-up continued via linkage to the National Death Index.

To better control for differences across studies, we allowed the baseline hazard function to vary across cohorts by implementing study-stratified Cox models. We tested for study heterogeneity by conducting likelihood ratio tests comparing models with and without study × powder interaction terms. For the primary analysis of ever vs never powder use and ovarian cancer risk, we additionally calculated the effect estimate and the *P* value for heterogeneity from a random-effects meta-analysis.[18] Proportional hazards assumptions were tested via likelihood ratio tests of powder × time interaction terms.

Because patency is required for there to be a direct physical pathway between the powder application area and the ovaries, we hypothesized a priori that women with patent reproductive tracts would be more susceptible to the effects of powder use in the genital area on ovarian cancer. We therefore conducted analyses restricted to this subgroup. When estimating the effects of duration of powder use on ovarian cancer risk, we compared long-term (≥20 years) and non-long-term users with never users. Similarly, we compared frequent users (≥1/week) and nonfrequent users with never users. We conducted trend tests using the ordinal forms of these variables.

We also conducted exploratory analyses to examine whether the association between powder use in the genital area and ovarian cancer varied by subgroup. These categorizations were selected based on the existing literature or hypotheses about potential biological mechanisms and included age, race/ethnicity, menopausal hormone therapy use, BMI, and parity. We also considered time-varying menopausal status and follow-up time as effect modifiers and more formally compared subgroups defined by hysterectomy, tubal ligation and patency status. We evaluated heterogeneity across strata of each potential effect modifier by conducting likelihood ratio tests of the interaction between that factor and powder use in the genital area.

For analyses limited to medically confirmed cases of ovarian cancer, we censored unconfirmed cases at their self-reported age of diagnosis. For type-specific analyses, the medically confirmed cases were further divided by invasiveness status (invasive vs borderline), tumor location (epithelial ovarian, peritoneal, or fallopian tube), or histotype (serous, endometroid, mucinous, clear-cell, or other). For an alternative histotype analysis, we defined high-grade

Table 1. Description of Participating Cohorts[a]

	Nurses' Health Study[b]	Nurses' Health Study II[c]	Sister Study[d]	Women's Health Initiative[e]	Total
Sample size	81 869	61 261	40 647	73 267	257 044
Included study period	1982-2016	2013-2017	2003-2017	1993-2017	1982-2017
Follow-up time, median (IQR), y	33.2 (20.0-34.0)	3.8 (3.5-3.9)	9.6 (8.4-11.1)	17.4 (8.7-19.9)	11.2 (3.9-21.0)
Age range at assessment for use of powder in the genital area, y	35-62	48-68	35-77	49-81	35-81
Age, median (IQR), y	48 (42-55)	58 (54-62)	55 (48-61)	63 (57-69)	57 (50-62)
All ovarian cancer cases	1258	76	220	659	2213
Medically confirmed ovarian cancer cases	1055	37	172	659	1923
Powder use in genital area, %					
Ever	41	26	27	53	39
Long-term		6	6	16	10
Frequent	27	26	7		22

Abbreviation: IQR, interquartile range.

[a] More detailed descriptions of the Nurses' Health Study and the Nurses' Health Study II can be found in Bao et al[14]; in Sandler et al[15] for the Sister Study; and in Anderson et al[16] for the Women's Health Initiative.

[b] Powder use in the genital area was assessed in the 1982 follow-up questionnaire, not at study baseline. Participants were excluded if they did not respond to the question regarding use of powder in the genital area (n = 28 584), had ovarian cancer prior to responding to the 1982 questionnaire (n = 174), underwent a bilateral oophorectomy at the time of the 1982 questionnaire (n = 10 896), or did not contribute any person-time after the 1982 questionnaire (n = 4). Frequent use was defined as use of powder in the genital area at least once per week. Women who underwent bilateral oophorectomy during follow-up were censored at age of oophorectomy. Follow-up was complete through June 1, 2016.

[c] Use of powder in the genital area was assessed in the 2013 follow-up questionnaire, not at study baseline. Participants were excluded if they did not respond to the question regarding use of powder in the genital area (n = 41 141), had ovarian cancer prior to 2013 (n = 287), underwent a bilateral oophorectomy at the time of the 2013 questionnaire (n = 13 739), or did not contribute any person-time after the 2013 questionnaire (n = 1). Frequent use was defined as use of powder in the genital area at least once per week. Long-term use was defined as use of powder in the genital area for 20 years or longer. Because data were reported in 2-year cycles, we did not censor for oophorectomy that occurred after 2013. Follow-up was complete through June 1, 2017.

[d] Participants were excluded if they withdrew from the study (n = 2), had ovarian cancer prior to baseline or unclear ovarian cancer status at baseline (n = 225), underwent a bilateral oophorectomy prior to baseline (n = 9009), or did not respond to any of the questions regarding use of powder in the genital area (n = 1001). Ever powder use was defined as use of powder in the genital area during the 12 months prior to baseline or at ages 10 to 13 years. Long-term use was defined as use of powder in the genital area at ages 10 to 13 years and within the last 12 months. Frequent use was defined as use of powder in the genital area at least once per week (during the last 12 months) or *frequently* (as termed in the questionnaire) between ages 10 and 13 years. Women who underwent a bilateral oophorectomy during follow-up were censored at age of oophorectomy. Follow-up was complete through September 15, 2017.

[e] Participants were excluded if they did not complete the questionnaire regarding use of powder in the genital area (n = 342), had ovarian cancer before baseline (n = 641) or unknown cancer status before baseline (n = 890), underwent a bilateral oophorectomy at baseline (n = 18 183), or had no follow-up information (n = 353). Long-term use was defined as use of powder in the genital area for 20 years or longer. Postbaseline oophorectomies were not recorded. Follow-up was complete through February 28, 2017.

serous as grades 2 to 4 serous or grades 3 to 4 endometroid tumors.[19] We estimated the HRs for each set of subtypes using joint Cox proportional hazards models,[20] utilizing likelihood ratio tests to compare model fit for models that did and did not allow the main-effect estimates to differ by subtype. These test results are reported as *P* values for heterogeneity.

In a sensitivity analysis, we attempted to isolate participants who were possibly exposed to asbestos-contaminated talc by limiting analysis to women in WHI-OS and NHS, most of whom were born before 1945. In the age-adjusted and fully adjusted models, we additionally estimated cumulative risk of ovarian cancer by age 70 years and assessed differences in absolute risk among ever vs never users of powder in the genital area using the Breslow method.[21]

Statistical tests were 2-sided, and a *P* value less than .05 was considered statistically significant. Because of the potential for type I error due to multiple comparisons, findings from subgroup and sensitivity analyses should be interpreted as exploratory. All analyses were conducted in SAS 9.4.

Results

After initial exclusions, we had data from 257 044 women, including 2213 who developed incident ovarian cancer (**Table 1**). Use of powder in the genital area was common overall (39%) but varied by cohort with 53% of participants reporting ever use in WHI-OS, 41% in NHS, 27% in SIS, and 26% in NHSII. Long-term use was reported by 16% in WHI-OS and by 6% in both SIS and NHSII; frequent use was reported by 27% in NHS, 26% in NHSII, and 7% in SIS.

After further excluding women with missing covariates (<3% of all participants), 2168 participants with ovarian cancer (1884 medically confirmed) and 250 577 without ovarian cancer remained. Most NHS and WHI-OS participants were born between 1915 and 1944 and most NHSII and SIS participants were born in 1945 or later (eTable 1 in the Supplement), and there appeared to be a generational trend in use of powder in the genital area, with older cohorts more

Table 2. Study-Specific and Pooled Risk Differences, Hazard Ratios, and 95% CIs for the Association Between Ever Use of Powder in the Genital Area and Risk of Ovarian Cancer

Cohort	Person-Years, No. at Risk[a]	No. Without Ovarian Cancer[a]	No. With Ovarian Cancer[a]	Incidence per 100 000 Person-Years[a]	Prevalence of Powder Use in the Genital Area, %[a]		Age-Adjusted RD (95% CI), %[a]	Adjusted RD (95% CI), %[a,b]	Adjusted HR (95% CI)[a,b]
					Without Ovarian Cancer	With Ovarian Cancer			
Ever Used Powder in the Genital Area, All Women									
NHS	2 130 797	79 055	1224	57	41	42	0.06 (−0.07 to 0.20)	0.09 (−0.06 to 0.24)	1.07 (0.95 to 1.20)
NHSII	220 658	60 464	76	34	26	24	−0.10 (−0.44 to 0.24)	−0.15 (−0.49 to 0.20)	0.81 (0.47 to 1.38)
SIS	376 212	40 193	219	58	27	29	0.14 (−0.28 to 0.56)	0.03 (−0.39 to 0.45)	1.02 (0.76 to 1.38)
WHI-OS	1 038 039	70 865	649	63	53	56	0.09 (−0.05 to 0.23)	0.09 (−0.05 to 0.24)	1.11 (0.95 to 1.30)
Pooled estimate[c]	3 765 706	250 577	2168	58	38	44	0.08 (−0.03 to 0.19)	0.09 (−0.02 to 0.19)	1.08 (0.99 to 1.17)[d]
Ever Used Powder in the Genital Area, Women With Patent Reproductive Tracts[e]									
NHS	1 408 991	52 191	850	60	41	44	0.22 (0.03 to 0.40)	0.22 (0.02 to 0.42)	1.16 (1.01 to 1.33)
NHSII	140 534	38 503	51	36	26	27	0.06 (−0.39 to 0.51)	−0.01 (−0.46 to 0.43)	0.98 (0.52 to 1.83)
SIS	226 866	24 080	116	51	25	23	−0.13 (−0.63 to 0.37)	−0.21 (−0.72 to 0.31)	0.84 (0.55 to 1.31)
WHI-OS	614 280	41 928	367	60	51	56	0.12 (−0.08 to 0.32)	0.11 (−0.08 to 0.30)	1.13 (0.92 to 1.39)
Pooled estimate[c]	2 390 672	156 702	1384	58	37	45	0.15 (0.01 to 0.30)	0.15 (0.01 to 0.29)	1.13 (1.01 to 1.26)[f]

Abbreviations: HR, hazard ratio; NHS, Nurses' Health Study; NHSII, Nurses' Health Study II; RD, risk difference; SIS, Sister Study; WHI-OS, Women's Health Initiative Observational Study.

[a] Data are reported among participants with complete covariate information. Includes all self-reported cases.

[b] Referent group is never users. Effect estimates and HRs for women with patency were adjusted for race/ethnicity (white, black, other), education (≤ high school, some college, ≥college graduate), body mass index (calculated as weight in kilograms divided by height in meters squared, [restricted cubic spline]), parity (0, 1, 2, ≥3 births), ever use for oral contraceptives, tubal ligation (yes or no), hysterectomy status (yes or no), menopausal status (premenopausal or postmenopausal), and ever use of hormone therapy. Only effect estimates were adjusted for tubal ligation status (yes or no) and for hysterectomy status (yes or no). All covariates indicate status at time of assessment for use of powder in the genital area. RDs were calculated based on estimated cumulative incidence of ovarian cancer by age 70 years.

[c] Pooled estimates were calculated using Cox proportional hazards models, stratified by study to allow for the baseline hazard functions to vary by cohort, and adjusted for the same covariates as the study-specific models.

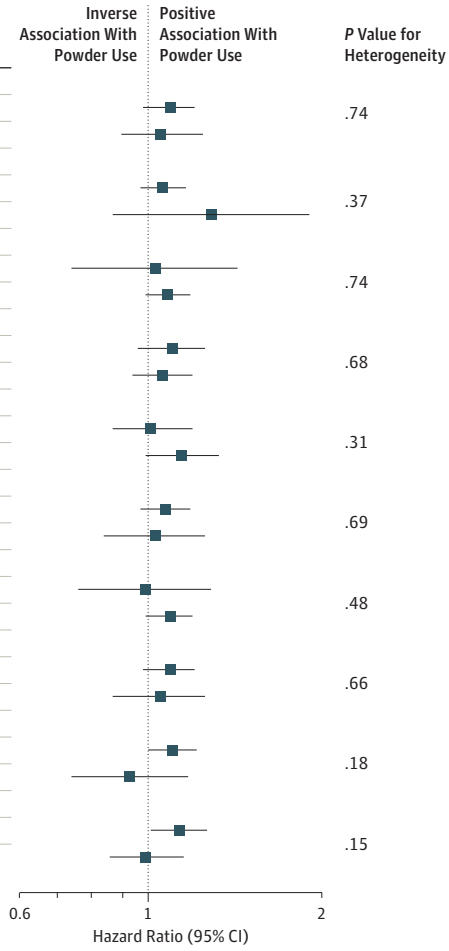
[d] The *P* value for heterogeneity between studies was .81 and was calculated using the likelihood ratio test for study by main-effects interaction term.

[e] Patency indicates having a uterus (ie, no hysterectomy) and no tubal ligation.

[f] The *P* value for heterogeneity between studies was .73 and was calculated using the likelihood ratio test for study by main-effects interaction term.

Figure. Subgroup Analyses for the Association Between Ever Use of Powder in the Genital Area and Risk of Ovarian Cancer, Pooled Hazard Ratios (HRs) and 95% CIs[a]

Characteristic	Participants With Ovarian Cancer, No.[b]	Hazard Ratio (95% CI)	P Value for Heterogeneity
Age, y			
<60	1533	1.09 (0.98-1.20)	.74
≥60	635	1.05 (0.90-1.24)	
Race/ethnicity			
Non-Hispanic white	2061	1.06 (0.97-1.16)	.37
Other	107	1.28 (0.87-1.90)	
Menopause status[c]			
Premenopausal	730	1.03 (0.74-1.42)	.74
Postmenopausal	1438	1.08 (0.99-1.18)	
Follow-up time, y			
0-10	954	1.10 (0.96-1.25)	.68
≥10	1214	1.06 (0.94-1.19)	
Hormone therapy[d]			
Never	654	1.01 (0.87-1.19)	.31
Ever	784	1.14 (0.99-1.32)	
Body mass index[e]			
<30	1757	1.07 (0.97-1.18)	.69
≥30	411	1.03 (0.84-1.25)	
Parity			
Nulliparous	252	0.99 (0.76-1.28)	.48
Parous	1916	1.09 (0.99-1.19)	
Hysterectomy			
No	1658	1.09 (0.98-1.20)	.66
Yes	510	1.05 (0.87-1.25)	
Tubal ligation			
No	1840	1.10 (1.00-1.21)	.18
Yes	328	0.93 (0.74-1.17)	
Patency			
Patent	1384	1.13 (1.01-1.26)	.15
Not patent	784	0.99 (0.86-1.15)	



[a] Adjusted for study, race/ethnicity (white, African American, other), education (<high school, some college, ≥college graduate), body mass index (BMI [calculated as weight in kilograms divided by height in meters squared], restricted cubic spline), parity (0, 1, 2, ≥3 births), ever use of oral contraceptives, tubal ligation (yes or no), hysterectomy (yes or no), menopausal status (premenopausal or postmenopausal), ever hormone therapy use. When estimating HRs within a strata of a variable, that variable was not included in the adjustment set.

[b] Numbers include only participants with complete covariate information.

[c] Effect estimate based on menopausal status updated throughout follow-up. Of the 2168 cases, 165 were diagnosed while the participant was premenopausal and 2003 occurred after menopause.

[d] Among women who were postmenopausal at baseline.

[e] Calculated as weight in kilograms divided by height in meters squared.

likely to report use. Overall, this was a highly educated group (most completed college) and most participants were white (84%-98% of each cohort). Compared with never users, ever users of powder in the genital area were more likely to be black (6% vs 3%; eTable 2 in the Supplement), to be obese (26% vs 19%), or to have had a hysterectomy (22% vs 18%), and less likely to have used oral contraceptives (57% vs 64%).

A total of 2168 women developed ovarian cancer (58 cases per 100 000 person-years; **Table 2**). Consistent with mean age at enrollment, incidence was highest in WHI-OS (63 cases per 100 000 person-years) and lowest in NHSII (34 cases per 100 000 person-years). In the pooled sample, estimated crude cumulative incidence of ovarian cancer at age 70 years was 1.3%, with higher risk among participants in NHS (1.3%) and SIS (1.4%) than in NHSII (0.7%) or WHI-OS (0.9%).

Considering all 4 cohorts, the estimated incidence of ovarian cancer was 61 per 100 000 person-years among ever users and 55 among never users. The estimated adjusted cumulative risk of ovarian cancer by age 70 years among unexposed participants was 1.16%, with an estimated covariate-adjusted risk difference of 0.09% (95% CI, −0.02% to 0.19%) comparing with those who were exposed. The HR for the association between ever powder use and incident ovarian cancer was 1.08 (95% CI, 0.99 to 1.17; Table 2). There was no evidence of heterogeneity across cohorts (*P* value for heterogeneity = .81) and no evidence of a proportional hazards assumption violation (*P* > .99). The estimated HR from the random-effects model was 1.07 (95% CI, 0.98 to 1.17; *P* value for heterogeneity = .71).

When restricted to women with patent reproductive tracts at baseline, the HR was 1.13 (95% CI, 1.01 to 1.26) and the estimated covariate-adjusted risk difference was 0.15% (95% CI, 0.01% to 0.29%). Among women without patent reproductive tracts, the estimated HR was 0.99 (95% CI, 0.86 to 1.15) and the *P* value for heterogeneity comparing the result for women with patency vs without was .15 (**Figure**). The remaining stratified analyses are also presented in the Figure and in eTable 3 in the Supplement.

The covariate-adjusted risk difference for long-term (≥20 years) vs never use was 0.01% (95% CI, −0.21% to 0.24%), and the HR was 1.01 (95% CI, 0.82 to 1.25; *P* value for trend = .57; **Table 3**). The covariate-adjusted risk difference for frequent use (≥1/week) vs none was 0.10% (95% CI, −0.05% to 0.25%), and the HR was 1.09 (95% CI, 0.97 to 1.23; dose-response

Table 3. Study-Specific and Pooled Risk Differences, Hazard Ratios, and 95% CIs for the Association Between Duration and Frequency of Powder Use in the Genital Area and Risk of Ovarian Cancer

Powder Use in the Genital Area	Person-Time at Risk[a]	Noncases[a]	Ovarian Cancer Cases[a]	Incidence per 100 000 Person-Years[a]	Prevalence of Powder Use[a], %		Age-Adjusted RD (95% CI), %[a]	Adjusted RD (95% CI), %[a,b]	Adjusted HR (95% CI)[a,b]	*P* Value for Heterogeneity[c]	*P* Value for Trend[d]
					Noncases	Cases					
All Women											
Long-term use[e]											
NHSII	220 658	60 464	76	34	6	5	−0.11 (−0.71 to 0.49)	−0.18 (−0.77 to 0.41)	0.76 (0.27 to 2.10)		
SIS	376 212	40 193	219	58	6	5	−0.07 (−0.85 to 0.70)	−0.21 (−0.95 to 0.53)	0.85 (0.46 to 1.57)		
WHI-OS	1 034 453	70 598	649	63	16	15	0.04 (−0.16 to 0.24)	0.05 (−0.15 to 0.26)	1.06 (0.85 to 1.34)		
Pooled estimate[f]	1 631 323	171 255	944	58	10	12	0.01 (−0.24 to 0.25)	0.01 (−0.21 to 0.24)	1.01 (0.82 to 1.25)	.90	.49
Used powder ≥1/wk											
NHS	2 130 797	79 055	1224	57	27	29	0.12 (−0.04 to 0.28)	0.14 (−0.04 to 0.31)	1.11 (0.97 to 1.26)		
NHSII	220 658	60 464	76	34	26	24	−0.10 (0.44 to 0.25)	−0.15 (−0.49 to 0.20)	0.81 (0.47 to 1.38)		
SIS	376 212	40 193	219	58	7	9	0.52 (−0.32 to 1.35)	0.35 (−0.46 to 1.15)	1.25 (0.78 to 2.00)		
Pooled estimate[f]	2 727 667	179 712	1519	56	22	26	0.11 (−0.05 to 0.26)	0.10 (−0.05 to 0.25)	1.09 (0.97 to 1.23)	.65	.20
Women With Patent Reproductive Tracts[g]											
Long-term use[e]											
NHSII	140 534	38 503	51	36	6	4	−0.20 (−0.91 to 0.51)	−0.30 (−0.94 to 0.35)	0.59 (0.14 to 2.47)		
SIS	226 866	24 080	116	51	5	5	−0.04 (−1.05 to 0.97)	−0.14 (−1.14 to 0.85)	0.89 (0.39 to 2.05)		
WHI-OS	612 086	41 770	367	60	15	15	0.05 (−0.24 to 0.33)	0.05 (−0.22 to 0.33)	1.06 (0.78 to 1.44)		
Pooled estimate[f]	979 486	104 353	534	54	9	12	0.01 (−0.31 to 0.32)	0.00 (−0.29 to 0.30)	1.00 (0.76 to 1.32)	.81	.66
Used powder ≥1/wk											
NHS	1 408 991	52 191	850	60	27	31	0.28 (0.06 to 0.49)	0.29 (0.05 to 0.52)	1.21 (1.04 to 1.41)		
NHSII	140 534	38 503	51	36	26	27	0.06 (−0.39 to 0.51)	−0.01 (−0.46 to 0.43)	0.98 (0.52 to 1.83)		
SIS	226 866	24 080	116	51	6	8	0.33 (−0.74 to 1.41)	0.20 (−0.84 to 1.25)	1.15 (0.58 to 2.31)		
Pooled estimate[f]	1 776 391	114 774	1017	57	22	28	0.25 (0.04 to 0.46)	0.22 (0.02 to 0.42)	1.19 (1.03 to 1.37)	.69	.03

Abbreviations: HR, hazard ratio; NHS, Nurses' Health Study; NHSII, Nurses' Health Study II; RD, risk difference; SIS, Sister Study; WHI-OS, Women's Health Initiative Observational Study.

[a] Data are reported among participants with complete covariate information. Includes all self-reported cases.

[b] Referent group is never users. Effect estimates are adjusted for race/ethnicity (white, black, other), education (≤high school, some college, ≥college graduate), body mass index (calculated as weight in kilograms divided by height in meters squared, [restricted cubic spline]), parity (0, 1, 2, ≥3 births), ever use of oral contraceptives, tubal ligation (yes or no), hysterectomy status (yes or no), menopausal status (premenopausal or posmenopausal), and ever use of hormone therapy. All covariates indicate status at time of assessment for use of powder in the genital area. RDs were calculated based on estimated cumulative incidence of ovarian cancer by age 70 years.

[c] Likelihood ratio test for study by main-effects interaction term.

[d] A test of the β coefficient for considering frequency (no use, nonfrequent use, frequent use) or duration (no use, non–long-term use, long-term use) of powder as an ordinal variable.

[e] See eAppendix in the Supplement for study-specific definitions of long-term use.

[f] Pooled estimates were calculated using Cox proportional hazard models, stratified by study to allow for the baseline hazard functions to vary by cohort, and adjusted for the same covariates as the study-specific models.

[g] Patency indicates having a uterus (ie, no hysterectomy) and no tubal ligation.

Table 4. Pooled Hazard Ratios and 95% CIs Among Medically Confirmed Cases Overall and by Tumor Invasiveness, Location, and Histotype

	No. of Cases[a]	Hazard Ratio (95% CI)		
		Ever Use[b]	Long-term Use[b]	Frequent Use[b]
All medically-confirmed cases	1884	1.05 (0.96-1.16)	1.03 (0.83-1.28)	1.05 (0.92-1.20)
Invasiveness level				
Invasive only	1538	1.07 (0.97-1.19)	1.08 (0.85-1.37)	1.08 (0.93-1.25)
Borderline	139	1.09 (0.79-1.52)	1.31 (0.59-2.92)	0.98 (0.60-1.60)
P value for heterogeneity[c]		.90	.41	.31
Tumor location				
Epithelial ovarian	1536	1.08 (0.97-1.19)	1.08 (0.85-1.37)	1.09 (0.94-1.27)
Fallopian tube	52	1.19 (0.69-2.08)	2.18 (0.46-10.3)	1.35 (0.69-2.65)
Peritoneal	103	1.12 (0.76-1.65)	1.18 (0.33-4.16)	0.76 (0.44-1.31)
P value for heterogeneity[c]		.92	.58	.02
Histotype				
Serous	1038	1.10 (0.97-1.25)	1.02 (0.75-1.38)	1.07 (0.90-1.28)
Endometroid	157	1.15 (0.83-1.58)	1.14 (0.49-2.63)	1.17 (0.76-1.79)
Mucinous	102	1.03 (0.69-1.54)	1.35 (0.58-3.15)	1.27 (0.73-2.22)
Clear Cell	68	1.17 (0.73-1.89)	1.01 (0.35-2.95)	1.11 (0.55-2.24)
Other	357	0.97 (0.79-1.20)	1.24 (0.79-1.94)	0.93 (0.68-1.27)
P value for heterogeneity[c]		.86	.97	.76
Histotype II[d]				
High-grade serous	732	1.08 (0.93-1.25)	0.99 (0.70-1.40)	1.05 (0.84-1.31)
Low-grade serous	29	1.41 (0.70-2.82)	1.25 (0.17-9.25)	0.70 (0.23-2.09)
Other	601	1.01 (0.86-1.19)	1.19 (0.84-1.69)	1.04 (0.82-1.32)
P value for heterogeneity[c]		.64	.78	.31

[a] Includes ever-use analysis; limited to women with complete covariate information.

[b] Referent group is never users. Adjusted for study, race/ethnicity (white, African-American, other), education (≤high school, some college, ≥college graduate), body mass index (calculated as weight in kilograms divided by height in meters squared, [restricted cubic spline]), parity (0, 1, 2, ≥3 births), ever use of oral contraceptives, tubal ligation (yes or no), hysterectomy status (yes or no), menopausal status (premenopausal or postmenopausal), ever use of hormone therapy.

[c] From competing risks model: likelihood ratio test of model that allows effect estimate to vary by subtype compared with a model that does not.

[d] High-grade serous indicates grades 2 to 4 serous or grades 3 to 4 endometroid; low-grade serous indicates grade 1 serous.

P value for trend =.20). The covariate-adjusted risk difference for the association between frequent powder use and ovarian cancer among women with patent reproductive tracts was 0.22% (95% CI, 0.02% to 0.42%), and the HR was 1.19 (95% CI, 1.03 to 1.37; *P* value for trend = .03).

When the outcome was limited to medically confirmed cases, the HR was attenuated (**Table 4**; HR, 1.05 [95% CI, 0.96 to 1.16] for ever use vs never use). There were no notable differences in estimates by invasive status, tumor location, or histotype. This was also true for analyses limited to women with patent reproductive tracts (eTable 4 in the Supplement). When limited to the older cohorts (NHS and WHI-OS), the estimated pooled HR was 1.09 (95% CI, 0.99 to 1.19) for ever use vs never use. The estimated HR from the young cohorts (NHSII and SIS) was 0.97 (95% CI, 0.75 to 1.26).

Discussion

In this pooled analysis of 4 large US cohorts, there was no statistically significant association between self-reported use of powder in the genital area and risk of ovarian cancer. There were no clear dose-response trends for duration and frequency of powder use in the genital area in relation to ovarian cancer risk. Although the study was underpowered to detect small changes in risk, this is, to our knowledge, the largest study of this topic to date, and it is believed that no other large prospective cohorts have collected data on powder exposure in the genital area.

One of the primary drivers of research on genital use of talc-based products and ovarian cancer has been the potential link between talc and asbestos, which can occur together in nature. In an analysis limited to the older cohorts in which women may have started using powder before the asbestos ban of 1976, the estimated effect remained consistent, with no association observed in the younger cohorts. However, it was recently suggested that some products may have contained asbestos after 1976, meaning that there may not be a clearly defined time period in which talc-based products did or did not contain asbestos.[22] Further, although most cosmetic powder products include some quantity of mineral talc,[1] the percentage varies widely,[23] and exposure to asbestos (through talc) would also depend on the type of product used and the method of application (eg, underwear vs diaphragm).

By irritating epithelial ovarian tissue or fallopian tubes[24] directly, powder could induce an inflammatory response even in the absence of asbestos. This could set off a cascade of increased oxidative stress levels, DNA damage, and cell division, all of which could contribute to carcinogenesis.[25] In this analysis, there was a possible positive association among women with patent reproductive tracts (no history of hysterectomy or tubal ligation), although because the association was not significantly different from that observed in women with nonpatent reproductive tracts, this finding should be considered only exploratory and hypothesis generating. This observation lends support to the hypothesis that powder with or without asbestos could irritate and inflame the reproductive

tract, as patency is required for there to be a direct physical path between the genitals and the fallopian tubes or ovaries.[26] The positive relationships between pelvic inflammatory disease and ovarian cancer[27] and chlamydia infection and ovarian cancer[28] also support an inflammation-mediated mechanism, as does the inverse association between regular aspirin use and ovarian cancer.[29]

One of the main concerns about previous case-control studies on this topic is the possibility for recall bias, which would result if case participants were more likely to report using powder than control participants. As highlighted by Trabert,[7] the African American Cancer Epidemiology Study[6] found evidence supporting this phenomenon. Based on the timing of the first major talc lawsuits,[30] Schildkraut et al[6] stratified their results by year of interview (earlier than 2014 vs 2014 or later), observing that among women interviewed earlier, ever use of powder in the genital area was less-strongly associated with ovarian cancer (odds ratio [OR], 1.19 [95% CI, 0.87 to 1.63]) than among women interviewed later (OR, 2.91 [95% CI, 1.70 to 4.97]). This difference was driven by an increase in the reported prevalence of powder use among case participants (36.5% vs 51.5% of women interviewed early vs later), while self-reported use in the control partcipants remained stable (34.0% vs 34.4%). However, most of the case-control studies that have examined this association recruited well before 2014, and a large pooled analysis published in 2013 reported an OR of 1.24 (95% CI, 1.15 to 1.33).[4] For the current analysis, recall bias was avoided by excluding those with preexisting ovarian cancer.

The strengths of this study were large sample size and long follow-up time. The main analysis included 2168 ovarian cancer cases that developed over 3.8 million person-years. This far exceeds a previous meta-analysis of the published NHS, SIS, and WHI-OS results (890 cases over 182 000 person-years).[5] However, power to investigate links to peritoneal or fallopian tube cancers or histotypes other than serous was still low. Improvements in the classification of tumor types may contribute new insights, especially for fallopian tube cancers, which may be the true point of origin for most serous ovarian cancers.[24] This and other subtype-specific associations should be better examined in the future.

Limitations

This study has several limitations. First, the included cohorts varied widely in how they assessed exposure, particularly the duration and frequency of powder use. There was no evidence of between-study heterogeneity for either the pooled or meta-analysis models of ever use vs never use, but because the 2 largest studies were missing information on duration (NHS) and frequency (WHI-OS) of powder use, the dose-response analyses are underpowered compared with the main results and thus difficult to interpret. Second, use of powder in the genital area could not be assessed as a time-varying factor, as none of the 4 studies collected data on use after baseline.

Third, specific exposure windows could not be examined, nor could type of powder used or patency status at time of powder use. As previously noted, information on powder exposure is typically more limited in cohort studies compared with case-control studies, particularly with respect to dose and duration of use.[31] Therefore, ongoing or future cohort studies should collect detailed information on these topics.

Fourth, as with all observational studies, residual confounding is possible. All 4 included studies recorded detailed information on many potential confounders, which were harmonized across cohorts and adjusted for in multivariable models. However, residual confounding may still be present if the harmonized covariates did not adequately capture the relationship or if any key confounders were missing.

Fifth, the study may have limited generalizability. All 4 cohorts included predominately white, well-educated women, approximately half of whom had a BMI of less than 25, which could raise concerns about generalizability, especially since these factors may be related to powder use. However, these studies have high retention rates and accurate self-reported data, increasing internal validity.

Sixth, confounding by indication is another potential limitation, and it would occur if women with other underlying conditions that were associated with ovarian cancer were also more likely to use powder in the genital area. It is also possible that if powder use is associated with increased risk of other gynecologic conditions (eg, fibroids, ovarian cysts), it can affect whether women receive oophorectomies, hysterectomies, or tubal ligations and alter their risk of developing ovarian cancer. Seventh, because tests to confirm patency were not performed, it is possible that not all women categorized as having a patent reproductive tract in this analysis had truly patent tubes.

Conclusions

In this analysis of pooled data from women in 4 US cohorts, there was not a statistically significant association between self-reported use of powder in the genital area and incident ovarian cancer. However, the study may have been underpowered to identify a small increase in risk.

ARTICLE INFORMATION

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Author Affiliations: Epidemiology Branch, National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina (O'Brien, Sandler); Department of Cancer Epidemiology, H. Lee Moffitt Cancer Center and Research Institute, Tampa, Florida (Tworoger); Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, Massachusetts (Tworoger); Program in Epidemiology, Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, Seattle, Washington (Harris); Department of Epidemiology, School of Public Health, University of Washington, Seattle (Harris); Public Health Sciences Division, Fred Hutchinson Cancer Research Center, Seattle, Washington (Anderson); Biostatistics and Computational Biology Branch, National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina (Weinberg); Metabolic Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, Rockville, Maryland (Trabert); Department of Obstetrics and Gynecology, University of Florida College of Medicine-Jacksonville (Kaunitz); Social and

Scientific Systems, Inc, Durham, North Carolina (D'Aloisio); Clinical Genetics Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, Rockville, Maryland (Wentzensen).

Author Contributions: Dr O'Brien had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Joint senior authors: Drs Sandler and Wentzensen.
Concept and design: O'Brien, Tworoger, Sandler, Wentzensen.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: O'Brien, Weinberg, Trabert, Wentzensen.
Critical revision of the manuscript for important intellectual content: O'Brien, Tworoger, Harris, Anderson, Trabert, Kaunitz, D'Aloisio, Sandler, Wentzensen.
Statistical analysis: O'Brien, Tworoger, Harris, Trabert.
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Supervision: Sandler, Wentzensen.

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